Atomic Energy Control Board
P.O. Box 1046
Ottawa, Canada
K1P 5S9

Commission de contrôle de l'énergie atomique
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K1P 5S9

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# TRANSPORT OF COMPOUNDS FROM MOTHER TO FOETUS

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by

B.M. Bowen, E.S. Garnett,
D.G. Perrier and W. Prestwich

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**Research report**

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A report prepared by B.M. Bowen, E.S. Garnett, D.G. Perrier and W. Prestwich, McMaster University and the Faculty of Pharmacy, University of Toronto, under contract to the Atomic Energy Control Board.

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ABSTRACT

This study reviews the literature and investigates the transport of selected radiopharmaceuticals from the mother to the foetus and the distribution of these radiopharmaceuticals in both animals and man. This search emphasizes the placental transport of the drugs from the mother to the foetus and the development of pharmacokinetic models that could describe this transport. An outline of the distribution and/or transport of several radiopharmaceuticals is presented followed by a description of the factors that regulate the transport of the radiopharmaceuticals from the mother to the foetus. Pharmacokinetic models were designed on the available information in the open literature. The limitation of the literature is discussed and suggestions for future experimental investigation are made.

RÉSUMÉ

La présente étude examine la documentation concernant le passage de certains produits radiopharmaceutiques de la mère au foetus et la distribution de ces produits chez les animaux et chez les humains. L'étude porte surtout sur le passage transplacentaire des médicaments de la mère au foetus et sur l'élaboration de modèles pharmacocinétiques pour le décrire. Elle donne un aperçu de la distribution et du passage de plusieurs produits radiopharmaceutiques, ainsi qu'une description des facteurs qui influent sur le passage de ces produits de la mère au foetus. Les modèles pharmacocinétiques ont été conçus à partir des renseignements disponibles dans la documentation non classifiée. Les auteurs signalent le caractère limité de la documentation et font des suggestions en vue d'autres vérifications expérimentales.

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# TRANSPORT OF COMPOUNDS FROM MOTHER TO FOETUS

## 1. INTRODUCTION

This report reviews and assesses the open literature on a) the transport of selected radiopharmaceuticals from the mother to the foetus, and b) the distribution of these radiopharmaceuticals within the foetus both in animals and in man. Pharmacokinetic models are presented which allow one to describe the time course of these compounds in the foetus.

The radiopharmaceuticals for study were selected by AECB and these are listed in Table I of this report. Sections 2 to 4 of this report identify the significant studies which pertain to each compound and discusses the limitations of the published studies. Sections 5 to 7 present a comprehensive overview of the processes that regulate the transport of these compounds and a series of models that might be used to describe the transport of a radiopharmaceutical from the mother to the foetus. Section 8, discusses the mathematics of the pharmacokinetic models. The scope and the limitations of the study and the models are outlined in a final discussion section.

## 2. LITERATURE SEARCH

The open literature was surveyed for each of the compounds listed in Table I. In order to provide a foundation for the search, the databases of the National Institutes of Health, National Library of Medicine, Chemical Abstracts, International Pharmaceutical Abstracts, and Toxnet were used. Whenever possible the search was repeated for the non-radioactive analogues of the compound/element. In each case the search concentrated on the following areas:

i) maternal-foetal exchange
ii) placenta
iii) biodistribution
iv) metabolism
v) pharmacokinetic characteristics.

After obtaining the primary references on each topic the secondary and tertiary references were investigated.

In order to meet the ultimate objective of the study to develop a database and a general pharmacokinetic model to constitute the basis of a human foetal dosimetry subprogramme, it is necessary to develop pharmacokinetic models which describe the transport of the compound/element from the mother to the foetus. Even if references are not available for the transport mechanism, the distribution of the compound in the mother and the foetus are frequently available. This information will allow a kinetic model to be designed with the only missing link being the quantity of the compound/element crossing the placenta per unit time.

Information on each article of significant use to the study was entered into a database programme. Each article was categorized by compound/element and the type of information (maternal, foetal, kinetic, or distribution) contained in it. This allowed easy retrieval and tabulation. Supplementary articles were placed in the database if they were found to contain pertinent information for the development of the pharmacokinetic model.

## 3. RESULTS OF THE SURVEY OF THE OPEN LITERATURE

### 3.1 Maternal-Foetal Exchange

We were surprised by the lack of literature on the maternal-foetal transport of these compounds in the open literature. Often only a single article exists which will give a clue about the percentage of the compound/element that crosses the placenta. It appears that the interest in the evaluation of the maternal-foetal exchange for the listed compounds/elements is proportional to the likelihood that a young woman in her child-bearing years will require a nuclear medicine procedure. Since it is more likely that she would be examined for a thyroid

disorder than a stroke, iodide transport has been studied to a greater extent than the lipid soluble amines used to detect cerebrovascular accidents. Bone scans are more prevalent than kidney scans. We have examined over 170 articles which contain information suitable for the design of the pharmacokinetic models. These 170 citations do not include the large number of papers on iodohippurate distribution or on albumin metabolism. The total number of references to the areas of interest for each radiopharmaceutical are tabulated in Table I.

3.2 Foetal/placental accumulation and distribution

These areas are usually discussed in the same articles as those that contain information on the maternal-foetal exchange. Where few references exist for a particular exchange, the measurement of foetal accumulation of the compound/element is also poorly described or not described at all. The important information needed for this study is the proportion of the radiopharmaceutical that crosses the placental barrier per unit time. For each radiopharmaceutical, one well conducted study in the literature would be sufficient to allow us to complete the model for that drug.

3.3 Metabolism

There are more references to the metabolism of the several radiopharmaceuticals than are useful for the development of the pharmacokinetic model. This contrasts markedly with the few references (4 only) that will be useful in the design of a model for maternal-foetal exchange of iodohippurate. The information in this section is important for the development of the maternal distribution of the compound/elements from which the pharmacokinetic model may be designed.

3.4 Pharmacokinetics

In Section 3 we have only cited those references which provide equations for the description of the observed distribution of the compound/element. There is information in some of the metabolism articles which will complement these articles as we develop the models.

3.5 Database

A database programme was written to facilitate the collation of the information contained in the references. This information has been analysed and the results of this analysis are summarized in Table I. Since all of the references contained in the database are not cited in the text of this report, a complete list is provided in Appendix A.

## 4.0 ANALYSIS OF INDIVIDUAL COMPOUND/ELEMENT REFERENCES

4.1 Sodium Pertechnetate $^{99m}Tc$

The characteristics of the pertechnetate ion determine most of the potential maternal-foetal exchange of technetium-99m. This is true not only when the technetium-99m is used in the pertechnetate form as a radiopharmaceutical but also when $^{99m}TcO_4^-$ is considered as the metabolite of other radiopharmaceuticals that contain technetium-99m. All such radiopharmaceuticals when metabolized will release $^{99m}TcO_4^-$ which will follow the pharmacokinetics and distribution of that ion. To be of use to this project, the literature must therefore yield distribution data for pertechnetate ion, pharmacokinetic parameters and some indication of the amount of the ion that will cross the placenta into the foetus. Fortunately this information is available.

Of historic interest, the papers of McAfee (1964) and Beasley (1966) contain very good distribution data and target organ clearance figures. This work has been followed by several that

have looked at specific organ distribution (Jost 1987; Williams 1983 ; Gossage 1982). The work of Wegst (1983) is very important. The maternal-foetal exchange of the pertechnetate ion was examined in rats, and present good distribution and pharmacokinetic information. Additional papers examining the accumulation and the clearance of pertechnetate into the milk in goats and swine reproduce many of the earlier clearance curves and hence corraborate the earlier observations (Ennis 1988 ; Ennis 1989 ; Jones 1989 ; Mountford 1987; Gerber 1989). These papers, plus the additional citations listed in Appendix A, and the fact that the pertechnetate ion is actively transported into the thyroid, salivary glands, and gastric mucosa in a manner similar to the iodide ion, allow us to suggest that this radioisotope follows a unidirectional model from the mother to the foetus for the exchange of the pertechnetate ion between the maternal and the foetal systems.

4.2 Tc-99m Macroaggregated Albumin Injection

Macroaggregated albumin consists of particles of denatured albumin with a particle size range of from 10 to 60 $\mu$ and a mean particle size of 25 $\mu$. The particles are larger than the lumen of pulmonary capillaries and are trapped in those portions of the lung which is perfused with blood. These particles do not cross the placental membrane. Particles of a similar size have been used to measure the maternal placental blood flow (Lipshitz 1986). We have not documented the papers which illustrate macroaggregated albumin pulmonary distribution in Appendix A since they are too numerous to list. Of concern however is the metabolism of this compound and the release of the pertechnetate ion into the maternal circulation. The work describing the excretion of this compound into human breast milk (Rose 1990 ; Pittard 1982) may be used to estimate the pertechnetate actually present after an intravenous injection of the Tc-99m macroaggregated albumin. The quantity of the $^{99m}$Tc that

accumulates in the breast milk is determined from the sum of the unbound $^{99m}Tc$ in the initial injection plus the $^{99m}TcO_4^-$ produced by the metabolism of the Tc-99m macroaggregated albumin. Since the macroaggregated albumin does not appear in the milk or cross the placenta, all of the $^{99m}$ Tc in the breast milk will be present as $^{99m}TcO_4^-$ and thus the pertechnetate kinetic model may be used to calculate the amount of this radioactivity that may cross the placenta.

4.3 Tc-99m Sulphide Colloid Injection

There were no references describing maternal-foetal exchange of this colloid. It is assumed due to its size that technetium-99m sulphide colloid (500 millimicrometres) will not cross the intact placenta. However, at the later stages of gestation the placenta may develop breaks in the membrane. This is thought to be the source of the maternal blood cells found in the foetal circulation at term (Wegst 1987). After an intravenous dose of the colloid Thorotrast, the quantity found in the foetus was $10^{-3}$ to $10^{-6}$ less than that found when a soluble salt of thorium was injected into pregnant rats (Sikov 1987). It is unlikely that very much technetium-99m sulphide colloid will pass through the placenta to the foetus. Mahon *et al* (1973) have shown that one hour after the injection of the drug into the mother, the foetus of a rabbit contains 0.01% of an injected dose of $^{99m}Tc$. The colloid is trapped in the liver, spleen and bone marrow and remains there at least long enough for the technetium-99m to decay. Only $^{99m}TcO_4^-$ not bound to the colloid (usually less than 5%), will be present in the maternal circulation and this will follow pertechnetate kinetics and distribution.

4.4 Tc-99m Methylene Diphosphonate

Tc-99m methylene diphosphonate crosses the placenta and localizes in the foetal bone (Mahon 1973). The passage of the compound is a function of molecular size since the original bone scanning

radiopharmaceutical, Tc-99m polyphosphate, with a 46 chain phosphate, does not cross the placenta; but the diphosphonate Tc-99m EHDP crosses the placenta. The proportion of the administered dose that crosses the placenta is unknown but is thought to be low, and probably crosses by diffusion rather than by an active process. It is reasonable to estimate that the percentage of a dose of a diphosphonate that crosses the placenta and localizes in the foetal bone is less than the quantity of $^{99m}TcO_4^-$ found in the maternal bone, and could range from 0.5 to 1%. The maternal pharmacokinetic data is well presented by several investigators (Anger 1980; McCarthy 1989; Molloi 1989; Castronovo 1977). These articles combined with the biodistribution data in several other reports (Handeland 1989; Nicolay 1988; Worsfold 1988; Holland 1989) enable us to formulate the nature of the kinetic model for the distribution of this radiopharmaceutical. A general bi-directional model may be used for this drug but the high extraction efficiency in the foetal bone suggests that the return of the drug to the maternal side of the placenta will be minute.

4.5 Tc-99m Glucoheptonate Injection

We were unable to find any references which examined the proportion of a dose of Tc-99m glucoheptonate that crosses the placenta. There are several references which describe the biodistribution and the pharmacokinetics associated with glucoheptonate (Neuwelt 1986; Front 1988; Iosilevsky 1989) which will enable one to describe the maternal and foetal distribution. The rapid clearance of Tc-99m glucoheptonate by the kidney indicates that a uni-directional pharmacokinetic model from the mother to the foetus may be used.

4.6 Tc-99m DTPA Injection

This compound may be injected or inhaled. The chelates of DTPA do not cross the placenta (Zylicz 1975; Fisher 1975; Mays

1976). Since the compound is usually used for physiological studies, pharmacokinetic and biodistribution data is available (Ilowite 1989; Evander 1988; Meignan 1988; Torsello 1988; Cheema 1988).

4.7 Tc-99m HIDA Injection

No direct references to the iminodiacetic acid derivatives and maternal-foetal exchange were found. Similarities in structure with compounds such as cholic acid and tetracycline might help us with an estimation of the actual maternal-foetal exchange. One article (Winter 1979) showed that a related compound Tc-99m pyridoxylideneglutamate does cross the placenta and distributes in a similar manner in the foetus as in the mother. They estimated that the foetal activity was less than 5% of the dose given to the mother. There is no information available on which to base the selection of a pharmacokinetic model.

4.8 Tc-99m/I-131/I-125 Albumin Injection

Tc-99m albumin was not included in the Table I nor were its iodine-125 or 131 counterparts. Their frequency of use in fact, is greater in nuclear medicine practice in Canada than several of the compounds tabulated. Several articles would permit the design of models for this group of protein radiopharmaceuticals (Boyd 1983; Hickl 1970; Peterson 1989). Boyd has shown that iodinated albumin does not cross the placenta and indeed may be used to determine the fetal and cotyledonary albumin spaces. Any passage of radioactivity would be due to the passage of the metabolites ($^{99m}TcO_4^-$ or $^{131/125}I^-$). The pharmacokinetic model describing the transfer of these ions would be employed. In practical terms the quantity of radioactivity crossing the placenta into the foetus would be very, very low.

4.9 Tc-99m Dimercaptosuccinic acid and Tc-99m and I-123 Labelled Amines

No information regarding the maternal-foetal exchange of these compounds was located. The first compound is rarely used in Canada. Information on its biodistribution is available but an estimation of the percentage of the dose crossing the placenta would be difficult. A Tc-99m labelled amine (HMPAO) has been used in the labelling of lymphocytes, and for the measurement of cerebral blood flow generally in elderly stroke patients and in children with epilepsy. Pharmacokinetic information is available on maternal biodistribution but no studies of the maternal-foetal exchange have been reported and any model developed at this time would only contain estimates.

4.10 Gluconate and Pyrophosphate

Neither of these compounds are used regularly as labelled radiopharmaceuticals but rather as a method of placing stannous ion onto the erythrocyte. When Tc-99m Pyrophosphate Injection is used it localizes in necrotic heart tissue and it follows the kinetic and distribution patterns of the other diphosphates. When stannous pyrophosphate is injected as the means of placing the stannous ion onto the erythrocyte, this injection is followed by an injection of sodium pertechnetate Tc-99m. This $^{99m}$Tc(VII) is reduced and is subsequently bound to the cell. The radioactivity follows the distribution of the erythrocyte and does not cross the placenta. The amount of unbound pertechnetate ion in the circulation varies and follows the biodistribution and pharmacokinetic pattern of $^{99m}TcO_4^-$

4.11 Sodium Iodide I-131

Perhaps the most widely studied compound on the list is the iodide ion. Data is available for all facets of this study and the pharmacokinetic design. The models proposed by Johnson (1987) and Price (pre-print) were compared to determine which

radioisotope dosimetry model best described the maternal-foetal transport of iodide ion. Neither Johnson nor Price describes a pharmacokinetic model which could estimate the transfer of iodide from the mother to the foetus.

Several workers have described the maternal-foetal exchange of iodide in detail (Chapman 1948; Logothetopoulos 1956; London 1964; Evans 1967; Canning 1986).Mean clearance values for maternal-foetal iodide transfer of 10.9 $ml.min^{-1}$ has been determined by Canning. The metabolism of iodide in the foetal thyroid has been described by Aboul-Khair (1966). All of these studies have been performed during the last two trimesters of the pregnancy when the foetus was large enough to be studied. The transport of iodide from the mother to the foetus is best described by a uni-directional pharmacokinetic model.

4.12 I-131 Iodomethylnorcholesterol Injection

This compound although not licensed as a drug in Canada, is used periodically by several teaching hospitals. The information about the labelled form of cholesterol that would be useful in the design of the model is not available. Several articles describing the placental transfer of cholesterol are available. Pitkin (1972) has shown that the transfer of cholesterol is predominately uni-directional with less than 5% of a dose of cholesterol injected into the foetus returning to the mother. Khamsi (1972) showed that the specific activity of $^{3}H$-cholesterol injected into a pregnant baboon reached a plateau after 5 days and that the specific activity of the cholesterol in both the mother and the foetus was similar. For practical purposes a uni-directional pharmacokinetic model with a slow transfer rate of cholesterol may be used.

4.13 I-131 Iodohippurate Injection

There are many publications on the metabolism of

iodohippurate many of which contain valuable pharmacokinetic data. We were able to locate one article which describes the maternal-foetal exchange (Laakso 1968) of iodohippurate. Since there is evidence that a small quantity of the iodohippurate returns to the maternal circulation, a general pharmacokinetic model may be used to describe the transfer of this drug from the mother to the foetus.

4.14 I-131 Metaiodobenzylguanidine Injection

There were no studies of the maternal-foetal exchange reported for this compound. Detailed descriptions of the metabolism of the radiopharmaceutical are available but we are concerned that there will be difficulty in designing a suitable model because of the lack of information on maternal-foetal exchange.

4.15 Ga-67 Gallium Citrate Injection

Gallium citrate crosses the placenta and may be localized in the foetus (Mahon 1973; Newman 1978; Palestro 1986; Tyndall 1976; Otten 1973). Newman describes the localization of the compound in the placenta of a 19 week pregnant female being investigated for lymphocytic lymphoma. Mahon observed that the percentage of a dose of $^{67}Ga$ citrate that accumulates in the foetus of a rabbit one hour after injection is about 0.02% . Gallium citrate usually concentrates in the liver and spleen. There is some radioactivity in the bowel which gradually clears. This information would suggest that the transfer of gallium through the placenta is slow. There is not enough information in the literature to determine whether a general or a uni-directional pharmacokinetic model should be used.

4.16 Tl-201 Thallous Chloride

Gibson and Becker (1969) have described detrimental effects of thallous chloride on the foetus in several species. Because of

the teratogenicity of thallium sulphate, there has been an interest in the maternal-foetal exchange of this element (Rade 1982; Olsen 1982; Shennan 1988). There appears to be a marked thallium retention by both the maternal and foetal organs of the rat with approximately 10% of the foetal dose remaining 8 days after injection. The highest concentrations were in the foetal brain and the maternal muscle (Rade 1982). The pharmacological similarity of thallium to potassium would suggest that a general pharmacokinetic model should be used to describe its transfer from the mother to the foetus.

4.17 Xe-133 Xenon Gas

We were unable to find any references to the maternal-foetal exchange of radioactive xenon gas. There are studies which examine the cerebral blood flow of the foetus. All of these involve cannulation of the foetal cerebral artery, and although they give good pharmacokinetic data, they do not give us the clue as to whether or not the gas actually crosses the placenta (Einer-Jensen 1975; Purves 1969).

4.18 In-111 Indium Chloride

Indium-111 chloride is used in the labelling of blood products (leucocytes, granulocytes, platelets) for the localization of abscesses or for the determination of the life span of the blood cell. The indium is bound to a lipophilic ligand (hydroxyquinoline or tropolone) and is incubated with the blood component. After injection the blood component follows a variable distribution pattern that would be difficult to generalize in a model. Indium chloride when injected, or released from the blood component, rapidly binds to transferrin and very little of this protein crosses the placenta to the foetus (Mahon 1973). The use of $^{113m}$In for placental localization is well documented (Sharf 1971; Mair-Borst 1969; Grüberger 1979).

## 5. REGULATION OF THE TRANSPORT OF COMPOUNDS FROM MOTHER TO FOETUS

This section of the report presents a comprehensive overview of the processes that regulate the transport of the radiopharmaceutical compounds to and their retention in the foetus. Gestational age is considered. Models are used to illustrate the various ways the compounds listed in Table I are handled by the mother and the foetus. The pitfalls of extrapolating data from animals to humans and from chemical analogues to radiopharmaceuticals are discussed. The report concentrates on those processes that must be considered in the design of the pharmacokinetic model.

### 5.1 The Placenta

The human placenta may be described as a villous hemomonochorial type. It contains villi that are projections of foetal tissue surrounded by chorion. The villi are exposed to circulating maternal blood and it is on this surface that the exchange of nutrients and drugs occur (Parer 1987). The villi start to develop between 13 to 21 days after conception with the live foetal circulation being active at 21 days (Wegst 1987). The development of this placenta continues until the fifth month of pregnancy. Thereafter the placenta functions as a mature placenta for the remaining four months. After the fifth month the placenta may increase in weight only two to three fold whereas the foetus will increase in weight by ten fold. At term the placenta weighs about 500 grams and the foetus 3 kilograms. These variations in morphology and weight must be considered when interpreting foetal disposition data.

The nature of the transport membrane plays an important role in the movement of radiopharmaceuticals between the mother and the foetus. Several methods of transport are involved in the trans-placental transfer of radiopharmaceuticals. In the human there are three tissue layers; the foetal trophoblast, the foetal connective tissue and the endothelium of the foetal capillaries

separating the foetal blood from that of the mother. The foetal trophoblast consists of the cytotrophoblast and the syncytiotrophoblast. In the latter, placental metabolism occurs (Parer 1987).

The net permeability of the entire membrane is a function of both the permeability and the thickness of the epitheliochorial tissue and the connective tissue layers (Moore 1974). In the human, the maternal epithelium erodes and the placental chorion lies directly over it: hence the name haemomonochorial. In contrast, in the pig and sheep there is no erosion of the maternal epithelium and the term epitheliochorial has been applied. Pigs and sheep have thicker membranes which are less prone to breaks and have the potential for different permeability characteristics. Hence, the thinner membrane in the human would be expected to have a higher permeability than the membranes of the other two animals. In reality this may not have as much importance in the functional behaviour of the placenta since the diffusion of many substances occurs with ease across the membrane (Wegst 1987; Robinson 1988).

## 5.1.1 The Transplacental Transfer of Radiopharmaceuticals

The radiolabelled drugs cross the placenta by one or more of five basic mechanisms:

1. Diffusion
2. Active Transport
3. Bulk Flow
4. Pinocytosis
5. Breaks - Direct communication between maternal and foetal blood through breaks in the placental membrane.

Figure 1 illustrates placental blood flow and diffusion.

## 5.1.2 Diffusion

This is a passive process in which no energy is required. The radiopharmaceuticals which cross the membrane by simple diffusion do so based on the concentration gradient between the maternal circulation and that of the foetus. Ions such as pertechnetate cross by diffusion. Fatty acids, the respiratory gases, and $Na^+$ and $Cl^-$ are natural examples of diffusible materials (Parer 1987). Organic pharmaceuticals cross the placenta by diffusion but their net transfer may also be a function of blood flow (Wegst 1987). Diffusion transfer is governed by Fick's Law:

$$\textit{Rate of transfer} = \textit{permeability} \times \textit{area} \times \frac{\textit{concentration difference}}{\textit{membrane thickness}} \quad (1)$$

or:

$$\frac{dq}{dt} = KA\frac{dc}{dx} \quad (2)$$

When calculating the passage of drug from mother to the foetus, the following factors must be considered:

Concentration Difference:

i) Concentration of drug in the maternal arterial blood $C_m$

ii) Concentration of drug in the foetal arterial blood $C_f$

Permeability:

iii) Maternal intervillous space blood flow

iv) Foetal-placental blood flow

v) Diffusing capacity of the placenta for the drug (K)

Other Factors:

vi) Ratio of maternal to foetal blood flow

vii) Protein binding of the drug

viii) Geometry of the exchange surface (A)

ix) Metabolism of the drug in the placenta

x) Membrane thickness. (x)

Although the first two (i and ii) are most readily measured, it must be understood that the passage of drug from the mother to the foetus is the net result of all of the factors.

Ralston (1987) states that the importance of Fick's Law is its emphasis of the role of $C_m$, the maternal concentration of the drug. This is the one quantity that may be controlled by radiopharmaceutical design and/or dose regimen.

**The villous surface area** of the human placenta at term is approximately 11 $m^2$ (Parer 1987). The actual area of exchange is about 1.8 $m^2$ depending on the stage of gestation. The membrane thickness of the human placenta is approximately 3.5 $\mu$ . The permeability or the diffusion coefficient of the membrane is perhaps the most important factor in the diffusion of drugs. It is influenced by the lipid solubility, degree of drug ionization

(pKa), molecular weight, placental blood flow, placental aging, and the protein binding of the drug (Mirkin 1973). These will be discussed in greater detail later.

5.1.3 Active Transport

There is some active transport in the placenta. This requires energy to move substances against a concentration gradient. It is thought that the iodide ion is transferred by active transport (London 1964) Amino acids, water soluble vitamins, and some of the larger ions such as $Fe^{++}$ and $Ca^{++}$ are transported by this means. It has been suggested that there are transferrin receptors on the surface of the microvilli of the syncytrophoblasts which may transfer iron to human placental ferritin where it may be either stopped or transported further (Wegst 1987). Of the radiopharmaceuticals listed, gallium-67 citrate is the most likely to be transported by the ferritin mechanism where it acts as an iron analogue. Yaffe and Juchau (1974) report that there is some evidence for the presence of a $Mg^{++}$ -dependent $Na^{+}$ + $K^{+}$ -activated ATPase (ouabain sensitive) as well as a $Ca^{++}$ -ATPase (ouabain insensitive) enzyme in human placentas. They feel that this is interesting because of the apparent involvement of ATPase enzymes in the active transport of organic ions.

5.1.4 Bulk Flow

There is a passage of materials due to a hydrostatic or osmotic gradient. Parer (1987) states that water is transported this way and that it may carry some water soluble low molecular weight solutes with it.

5.1.5 Pinocytosis

Immune globulins, oil soluble vitamins and steroids are incorporated into cellular cytoplasm in small vesicles and are then transported across the membrane. It would appear that no

mechanism for transport of colloids exists. It has been shown that colloidal actinides do not cross the placental barrier (Sikov 1968).
Cholesterol is synthesized in the placenta and will also cross it from the maternal circulation. The cholesterol esters on the other hand do not appear to cross the placental membrane and in the foetal circulation these esters are formed by the transfer of a fatty acid from lecithin to cholesterol (Robertson and Sprecher 1968). They have also shown that in the pregnant rat about 80% of the placental cholesterol is derived from the maternal circulation whereas in the foetus this percentage drops to 50-70% at 12-23 days and 15-20% at the 20 day point.

5.1.6 Breaks in the Placental Membrane

Breaks may occur when the villi break off and enter the maternal circulation. This situation is more prevalent in the later stages of gestation. These breaks may permit the free entry of large molecules into the foetal circulation, eg. insulin bound to an antibody. They also permit foetal blood cells to enter the maternal circulation at term.

5.2 Factors Influencing Permeability

5.2.1 Lipid Solubility and Degree of Ionization (pKa)

The placenta is composed of lipoprotein and is thus similar to other mammalian membranes (Mirkin 1973). Radiopharmaceutical molecules that are lipophilic at physiologic pH will diffuse more rapidly across the membrane into the foetal circulation. Generally these radiopharmaceutical compounds exist in their non-ionized state at pH 7.4 . In contrast to bases with high pKa's, acids with low pKa's diffuse slowly (Mirkin 1975). Shifts in the acid-base balance in the placenta could alter the permeability of some compounds by causing shifts in their partition coefficient. $^{123}$I-iodoampthetamine is a good example of

one of these compounds. The partition coefficient decreases by a factor of 4 between pH 7.5 and 7.0 (Kung 1983). This is caused by protonation of the compound at the lower pH resulting in higher water solubility. As the pH rises and the non-ionized form becomes more dominant it becomes more lipophilic. The pH of the umbilical circulation is 0.1 to 0.15 pH units lower than that of the maternal circulation. Hence, when such a compound crosses the placental membrane, it will be less lipophilic on the foetal side and less able to pass back to the maternal circulation.

5.2.2 Molecular Weight

Compounds with molecular weights greater than 1000 are severely impeded in their passage across the membrane. Compounds with molecular weights greater than 500 appear to have slow diffusion rates. When the molecular weight is less than 500, the compound tends to cross the placenta more quickly depending on its state of ionization and lipophilicity (Mirken 1975). Robinson (1988) has compared the ratio of the uni-directional clearance to the diffusion coefficient in water ($K_w/D_w$) with the molecular radius (nanometres) of several radiotracers. The ratio was highest for $Na^+$ ion with the smallest molecular radius (0.2 nm) and lowest for I-125 Albumin with the highest molecular radius (3.6 nm). In general if the molecular radius was greater than 0.4 nm there was little or no diffusion. Below 0.4 nm the rate of diffusion varied by a factor of 5.

5.2.3 Placental Blood Flow

The transfer of drugs across the placenta is altered by haemodynamic changes in either the maternal or the foetal side of the placenta. The more lipid soluble the compound the more dependent will its permeability be on the maternal placental blood flow (Mirkin 1975). The foetal umbilical blood flow in the human is about 120 ml/min/kg of foetal body weight or 360 ml/min in the whole placenta (Parer 1987). The maternal uterine blood

flow has been estimated to be approximately 150 ml/min/kg of total gravid uterus or 700 ml/min for the whole uterus. Approximately 80% of the uterine blood flow perfuses the intervillous space (Ralston 1987). In the foetal lamb it has been shown that the foetal-placental flow represents approximately 50% of the combined foetal ventricular output. It has been assumed that the numbers for the human foetus are not too different.

Little is known about the effects of changes in the maternal blood flow on the passage of drugs to the foetus. In the foetus, secondary heart failure, erythroblastosis fetalis, or drug intoxication may severely reduce the foetal circulation and also the drug transfer rates (Mirkin 1973).

5.2.4 Placental Aging

As the placenta ages there is a decrease in the thickness of its trophoblastic epithelium. This represents a change in thickness from 25 $\mu$ early in gestation to 2 $\mu$ at term (Mirkin 1975). An increase in the rate of diffusion occurs as a result. Work on rodents suggests that the most rapid drug transfer occurs in the first and last trimesters (Mirkin 1973).

5.2.5 Protein Binding

Drugs that are tenaciously bound to plasma proteins and transferred by passive processes will be transferred less rapidly across the placenta than those which are unbound or loosely bound (Mirkin 1973). The amount of drug bound to maternal serum proteins tends to be greater than that occurring in foetal serum (Mirkin 1975).

## 6. PHYSIOLOGIC and METABOLIC CONSIDERATIONS

### 6.1 Maternal

There are several physiological changes which occur during pregnancy. When considering the design of pharmacokinetic models, some of these may become important in the calculation of

concentrations and flow rates in the mother. The plasma volume and extracellular fluid volume in the mother increase by 30-40% and thus there is a larger dilution factor to be considered when calculating $C_m$. There is a minimal increase in the red cell mass. Cardiac output increases 30-40% . In addition the glomerular filtration rate increase of approximately 50% must be considered when describing the clearance of radiopharmaceuticals which are excreted by filtration through the kidney. The slight decrease in hepatic function may affect the metabolism of the protein radiopharmaceuticals. In the case of I-125 fibrinogen, this will be offset by the increase in fibrinogen production after the third month of gestation. During pregnancy there are also changes in the carrying capacity of some proteins; such as thyroid binding globulin.

6.2 Foetal

The foetus differs from the neonate and the adult. The fat content of the foetus may be as low as 1% of body weight as compared to 16% in the baby at term. There is also a much higher proportion of extracellular fluid volume and total body water content in the foetus than in the older infant (Yaffe 1976). The glomerular filtration rate in the foetus is 30-40% that of the adult and the tubular secretion is only 20-30% of the adult value (Mirkin 1975).

This information must be considered along with the knowledge that the foetal oxidative capacity and glucuronidation are decreased (Yaffe 1976). It will be difficult to relate this information to the design of the pharmacokinetic model.

## 7. RADIOPHARMACEUTICAL PHARMACOKINETIC MODELS

When describing the localization of a radiopharmaceutical, the intact drug and its metabolites must be considered as separate entities. Ideally the disposition of parent

radiopharmaceutical and its metabolites could be described by a physiological pharmacokinetic model. The use of such a model requires that a number physiological parameters be available. These include flows, volumes, partition coefficients and mass transfer coefficients.

When it is possible to obtain the required physiological parameters (eg. flows,volumes, partition coefficients, mass transfer coefficients) physiological models may be used. Unfortunately a considerable amount of data is required to validate such a model. First the required parameters must be obtainable. Generally only average maternal parameters from the literature, for example, blood flows and tissue volumes are available. There are few, if any, foetal parameters available, and if they were they would be less useful than those of the mother due to changes caused by foetal growth. Even if average values are available in the literature, a number must be measured, namely partition coefficient and mass transfer coefficients as they are drug and metabolite specific. The use of average parameters has problems in that few animals are average, and hence, accurate description of the data can be difficult. Also, considerable experimentation is required to determine needed parameters and obtain an adequate number of tissue and fluid concentration time points to determine if the model fits the data. All tissues and fluids which take up a "reasonable" amount of the drug must be identified. With all of these difficulties physiological pharmacokinetic models, while ideal, are not very realistic. Unfortunately we were not able to locate enough information with respect to the foetal handling of the radiopharmaceuticals, or compounds, or their non radioactive analogues, to allow us to select or utilise the physiological pharmacokinetic model system.

A second approach would be to use compartmental pharmacokinetic models. A number of such compartmental models are provided based on what is known about the disposition of the various

radiopharmaceuticals.

First a qualitative general model was designed to illustrate the disposition of a radiopharmaceutical, its metabolites, and their transfer from the mother to the foetus (Figure 2). Variations on this qualitative general model are provided to represent the disposition of the different radiopharmaceutical groups (Figures 3 & 4).

Radiopharmaceuticals can be divided into three general catagories:

i) Those that cross the placenta.
ii) Those that do not cross but their metabolites cross.
iii) Those that do not cross and do not have metabolites that cross.

The models reflect these categories and allow the examination of any radiopharmaceutical to be conducted if the appropriate concentration versus time data are available.

The models separate the maternal and the foetal circulations for both the intact radiopharmaceutical and the metabolite(s) of the drug. A fifth and sixth compartment allows the amniotic fluid to be examined. It must also be understood that with the radiopharmaceutical, the primary metabolite will be the radioactive element. Also, the nature of radiopharmaceutical formulation is generally such that the amount of the non-radioactive portion of the pharmaceutical that crosses the placenta is too low to be measured and of little or no importance when examining potential chemical toxicity in the foetus. Some of the properties of specific radiopharmaceuticals were discussed in Section 4.

7.1 Figure 2 Qualitative General Model: Radiopharmaceuticals That Cross The Placenta

This model describes all situations where both the intact drug and its metabolite(s) cross the placenta. The foetus may also metabolize the intact drug. The metabolite and parent drug may be excreted into the amniotic fluid and may return to the foetus by ingestion of amniotic fluid and may be passed back through the placental membrane to the maternal circulation for eventual excretion. I-131 iodomethylnorcholesterol and I-131 iodohippurate may follow this model.

7.2 Figure 3 Radiopharmaceuticals That Do Not Cross The Placenta, But Their Metabolites Cross

This model describes the situation where the intact drug reaches the placental circulation but does not cross the placenta. Metabolites reach the maternal side of the placental circulation and cross to the foetal side. These metabolites, usually iodide or pertechnetate ions, follow the pathway for these ions in the foetus.

Tc-99m sulphide colloid, and Tc-99m macroaggregates are examples of this class.

7.3 Figure 4 Radiopharmaceuticals That Do Not Cross The Placenta

This model will only apply when a radiopharmaceutical is cleared by the kidney but does not cross the placenta. The rate of the intact drug clearance is sufficiently fast that almost no metabolites will be formed and hence none will cross the placental membrane to the foetus. Tc-99m DTPA follows this pattern.

## 8. THE MATHEMATICAL DESCRIPTION OF THE PHARMACOKINETIC MODELS

The diagrams outlined in Section 7 may be converted into simpler compartmental models, and mathematical expressions may be developed to describe the disposition of the radiopharmaceuticals between the mother and the foetus. While the exact model required to describe the deposition of radiopharmaceuticals in the maternal-foetal system will depend on the specific radiopharmaceutical, with few exceptions a four compartment model (see figure 5) and various modifications or simplifications of this model (figures 6 and 7) should adequately describe the majority of these compounds. In this four compartment model the drug is given to the mother by intravenous bolus injection, then equilibrates with the maternal extravascular tissues and fluids. Subsequently the radiopharmaceuticals are eliminated generally either via metabolism or via the kidneys.

The four compartments consist of:
a) the maternal circulation and tissues and fluids with which the radiopharmaceutical readily equilibrates. (Compartment 1)
b) the maternal tissue and fluids with which the radiopharmaceutical equilibrates more slowly. (Compartment 2)
c) the foetal circulation and tissues and fluids with which the radiopharmaceutical readily equilibrates. (Compartment 3)
d) the foetal tissues and fluids with which the radiopharmaceutical equilibrates more slowly. (Compartment 4)

Compartments 1 and 2 describe the disposition of the radiopharmaceutical on the maternal side of the placental membrane while compartments 3 and 4 refer to the foetus. The radiopharmaceutical crosses the placenta (is able to diffuse back to the mother) and assumes a distribution pattern in the foetus that is similar to that in the mother, ie: requires two compartments to characterize its disposition. It is again pointed out that this and subsequent models to be described are simplifications of the previous models as they only apply to the radiopharmaceutical itself. As has been discussed previously, frequently the metabolite is of primary interest; for these cases

another set of compartments for the metabolite is required.

In these models the number of exponentials required to describe the data is directly related to the number of compartments present. For example, the general model (Figure 5) to describe the intact drug (does not include the metabolites which may be radioactive) requires four exponents. While one could generate exponents and numbers for such a model, the numbers frequently become meaningless because with this approach, the minimum number of exponents required to accurately describe the data, (ie, the number of identifiable compartments based on plasma concentration versus time data) from a statistically justifiable point of view, is generally less than the four compartments in the model.

Therefore, it is only practical to use the simplest pharmacokinetic approach to describe the data. That is, determining the minimum number of exponentials required to accurately describe the data. While information about the general distribution, (volume of distribution), and elimination (clearance) characteristics of a radiopharmaceutical can be determined using such an approach, this approach does not necessarily yield values to which physiological meaning can be attached. This is particularly true for volumes of distribution. However, as mentioned previously, the amount of experimentation required to gain kinetic insight into radiopharmaceutical disposition through pharmacokinetic physiological models is considerable. Such experiments may not be realistic.

8.1 Pharmacokinetic Parameters for the General Model

The disposition of the radiopharmaceutical may be described by a four compartment model. Compartments 3 and 4 describe the foetal handling of the drug and might in some cases be thought of as a mirror of compartments 1 and 2. The foetus would be expected to clear the radiopharmaceutical less efficiently than the mother, however, the accumulation and the distribution characteristics may be expected to be more similar to that of the mother than the elimination characteristics. Compartment 2 in the mother, which

is generally never analyzed for non-radioactive drugs, may contain the well documented site of localization of most radiopharmaceuticals, and hence could provide valuable clues for the description of the foetal compartment 4. Variations in the rates based on gestational age and the size of the foetal extracellular fluid volume exist but are difficult to measure. It is very difficult to obtain experimental pharmacokinetic data to describe compartment 4 as venous lines would have to be established to sample the foetal radiopharmaceutical concentration.

8.1.2 Bidirectional Flux

The following equations describe the concentrations of the radiopharmaceuticals in the mother and the foetus in compartments 1 and 3.

$$\frac{dX_1}{dt} = k_{21}X_2 + k_{31}X_3 - (k_{12}+k_{13}+k_{10})X_1 \qquad (3)$$

$$\frac{dX_3}{dt} = k_{13}X_1 + k_{43}X_4 - (k_{34}+k_{31}+k_{30})X_3 \qquad (4)$$

Equations 5 and 6 are forms of the solutions of the differential equations.

$$C_1 = A_1e^{-\alpha_1 t} + A_2e^{-\alpha_2 t} + A_3e^{-\alpha_3 t} + A_4e^{-\alpha_4 t} \qquad (5)$$

$$C_3 = A_5e^{-\alpha_1 t} + A_6e^{-\alpha_2 t} + A_7e^{-\alpha_3 t} + A_8e^{-\alpha_4 t} \qquad (6)$$

Where $A_1$ to $A_8$ and $\alpha_1$ to $\alpha_4$ are complex functions of all eight microconstants ($k_{12}, k_{21}, k_{10}, k_{31}, k_{13}, k_{30}, k_{43}, k_{34}$) the intravenous dose administered, the volume of compartment 1 in the case of $C_1$ and

the volume of compartment 3 in the case of $C_3$ . (Appendix B)

8.2 The Unidirectional Flow Model

The second model (Figure 6) applies for all compounds that cross the barrier with a uni-directional flow, or in those situations where the quantity of drug returning from the foetus is so small that the net effect on the transport constant $K_{31}$ is minimal. This condition applies to many of the radiopharmaceuticals of interest to the Atomic Energy Control Board and to the major metabolites of many of them, which are $^{99m}TcO_4^-$ or $^{125/131}I^-$. In Figure 6 the concentration of the radiopharmaceutical in the maternal and the foetal compartments may be described as follows:

$$\frac{dX_1}{dt} = k_{21}X_2 - (k_{12}+k_{13}+k_{10})X_1 \qquad (7)$$

$$\frac{dX_3}{dt} = k_{13}X_1 + k_{43}X_4 - (k_{34}+k_{30})X_3 \qquad (8)$$

Equations 9 and 10 are forms of the solution of the differential equations.

$$C_1 = L_1e^{-\lambda_1 t} + L_2e^{-\lambda_2 t} \qquad (9)$$

$$C_3 = L_3e^{-\lambda_1 t} + L_4e^{-\lambda_2 t} + L_5e^{-\lambda_3 t} + L_6e^{-\lambda_4 t} \qquad (10)$$

Where $L_1$ to $L_6$ and $\lambda_1$ to $\lambda_4$ are functions of all seven microconstants, the intravenous dose administered, the volume of compartment 1 in the case of $C_1$, and the volume of compartment 3 in the case of $C_3$ . (Appendix C)

## 8.3 No Diffusion or Transport

There are some radiopharmaceuticals in which no maternal-foetal transfer occurs. In this case the maternal two compartment model will apply (Figure 7). The maternal time course of the drug should be able to be described by equation 9. However the meaning of $L_1$, $L_2$, $\lambda_1$ and $\lambda_2$ will be slightly different as $K_{13}$ will equal zero.

## 8.4 Testing the Models

In order to test the model and estimate the concentration in compartment 3 of the unidirectional flow model (Figure 6), data from the work of London (London 1964) was used. London measured the concentration of $^{131}I$ in the umbilical and maternal blood of the guinea pig. He clamped the umbilical cord and inserted an arteriovenous shunt thus producing a closed loop which prohibited the blood from going to the foetus. A small pump moved the blood in the loop and samples of the blood were taken for analysis of the $^{131}I$ content. In essence he was measuring placental transfer only (foetal disposition was not allowed in this experiment). First the maternal blood concentration of $^{131}I$ was plotted and the values for $L_1$, $L_2$ and $\lambda_1$ and $\lambda_2$ in equation 9 were calculated (Figure 8). This in turn enabled estimates of the microconstants to be made. The following equation was then derived to describe the concentration of $^{131}I$ in the loop ($C_L$) which had a volume ($V_L$).

$$C_L = \frac{K_{12}X_o}{V_L}\left[\frac{K_{21}-\lambda_1}{\lambda_1(\lambda_1-\lambda_2)}\right]e^{-\lambda_1 t} + \frac{K_{12}X_o}{V_L}\left[\frac{\lambda_2-K_{21}}{\lambda_2(\lambda_1-\lambda_2)}\right]e^{-\lambda_2 t} + \frac{K_{12}X_o}{V_L}\left[\frac{K_{21}}{\lambda_1\lambda_2}\right] \qquad (11)$$

A simulation of drug concentrations in the loop is presented in Figure 9. Reasonable agreement was obtained using the following values: $K_{12} = 0.0492\ min^{-1}$, $K_{21} = 0.0568\ min^{-1}$, $\lambda_1 = 0.1273\ min^{-1}$, $\lambda_2 = 0.0172\ min^{-1}$.

## 9. DISCUSSION

Because of the well recognized potential for radiation hazard, there have been few if any studies performed on pregnant women. Therefore, there are very few direct references to pharmacokinetic modelling for radiopharmaceutical doses in the literature. For the most part, the information available describes either the organ accumulation or a blood clearance curve for the radiopharmaceutical in the mother. If the foetus is mentioned, it is usually to report a static total body determination of the drug in the foetus usually one hour after the dose has been given to the mother.

The information in the literature allows the determination of the radiopharmaceutical in the mother and in some cases in the foetus. It however generally fails to provide any indication of the time course of the radiopharmaceutical in the foetus or the transport parameters controlling the passage of the drug from the mother to the foetus. Hence, little information is available on foetal exposure. On the other hand, the qualitative and the general pharmacokinetic models which describe this process may be developed.

With the limited amount of information available, the use of a compartmental pharmacokinetic model system seems most appropriate; a physiological pharmacokinetic model being too speculative without any quantitative supporting data available. Most of the studies on humans that pertain to maternal-foetal transport examine the pharmacology and pharmacokinetics of local and general anaesthetic agents used during labour. Unfortunately the experimental procedures used to determine the values that would support a physiological pharmacokinetic model are difficult and for some radiopharmaceuticals, impossible to determine. Boyd and Canning (1983) have made some physiological measurements in an attempt to explain the nature of the placenta. In their examination of sodium transport they determined placental blood flow and the sodium, Cr-EDTA, and the albumin distribution volumes in the placenta. If one uses their data or performs new experiments,

physiological pharmacokinetic models could be designed which would describe the maternal foetal transfer of a drug in a discrete region of the placenta. This analysis would not however answer the question as to the overall transport of the radiopharmaceutical from the mother to the foetus.

While the simplest pharmacokinetic compartmental model only gives a general description of the time course, it only demands knowledge of the foetal and maternal blood concentrations vs time; numbers that may be determined experimentally. The most important parameters to be determined are the concentration of the radiopharmaceutical in the foetal blood or maternal blood and the transport coefficient across the placental membrane.

## 10. CONCLUSIONS

1. Although experiments describing the pharmacokinetics and the distribution of radiopharmaceuticals in the mother are outlined in the literature, there are no data describing the maternal-foetal transfer kinetics or specific distribution in the foetus for any radiopharmaceutical studied other than for sodium iodide. Although many papers were examined (>300) only 170 contained information that could be used in the development of the pharmacokinetic model. These are catagorized in TABLE 1.

2. Although physiological pharmacokinetic models provide an excellent method of describing the time course of drugs, these models must use physiological data. This data pertaining to radiopharmaceuticals is not available in the literature.

3. Development of a physiological model of maternal-foetal transport is possible, but the experimental data required to obtain the necessary parameters would be costly. Double infusion studies could be performed at a reasonable cost and would provide an estimation of the rate of transplacental transfer for selected radiopharmaceuticals/radiocompounds. This information would permit the development of compartmental pharmacokinetic models

that require fewer parameters than physiological models.

4. The infusion experiments would have to be performed for three trimesters of gestation if possible. It would be important to take into account the type of placenta developed by the test animal. An animal with a hemochorial type of placenta similar to that of the human should be chosen. The sheep with an epitheliochorial placenta is usually used because its placenta is less likely to tear during surgery. The cannulation of the umbilical chord is necessary in order to obtain data for the pharmacokinetic model. If the chord and the vessels in the chord are not large enough then this would be impossible. Pharmacokinetic studies would be possible only during the late second and the third trimester of the pregnancy.

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125-136

# DIAGRAM OF PLACENTAL BLOOD FLOW AND DIFFUSION

$$\frac{dq}{dt} = \frac{KA(C_m - C_f)}{dx}$$

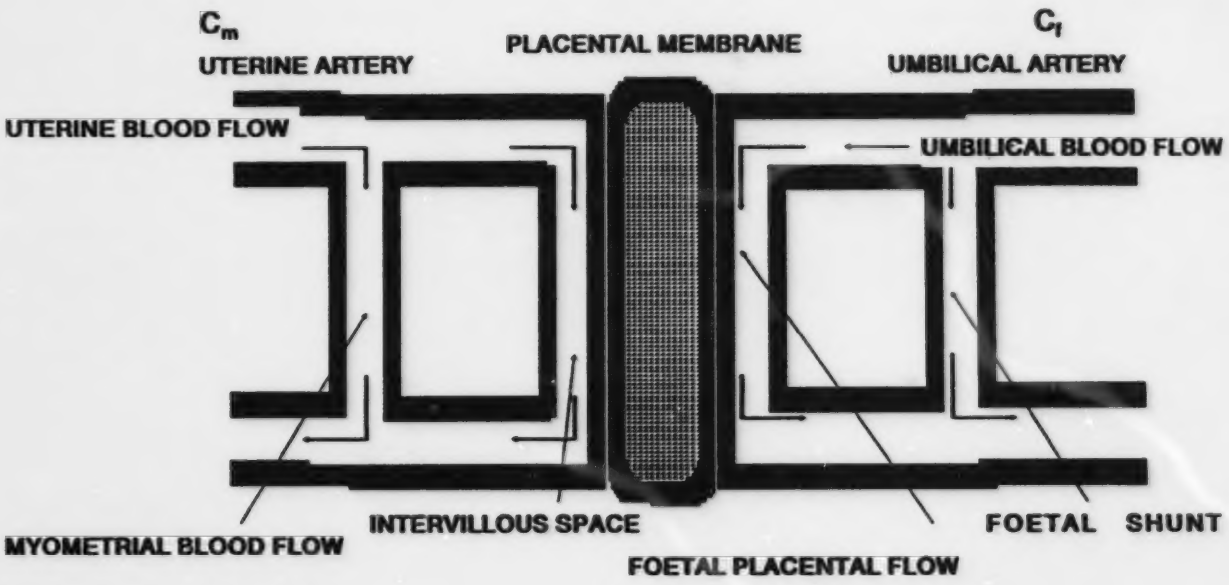


**FIGURE 1**

# GENERAL MODEL: RADIOPHARMACEUTICALS THAT CROSS THE PLACENTA

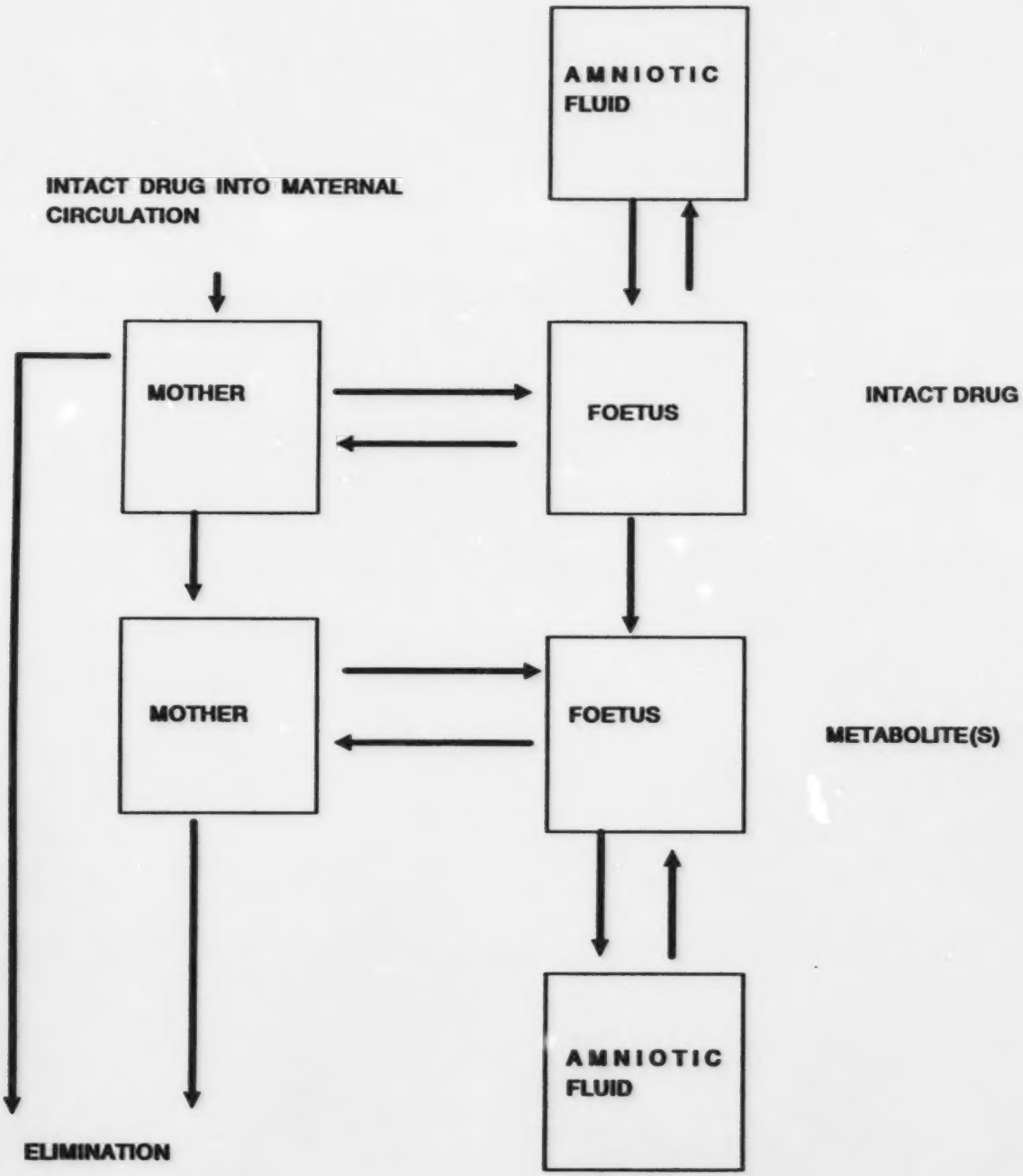


FIGURE 2

# RADIOPHARMACEUTICALS THAT DO NOT CROSS THE PLACENTA, BUT THEIR METABOLITES CROSS

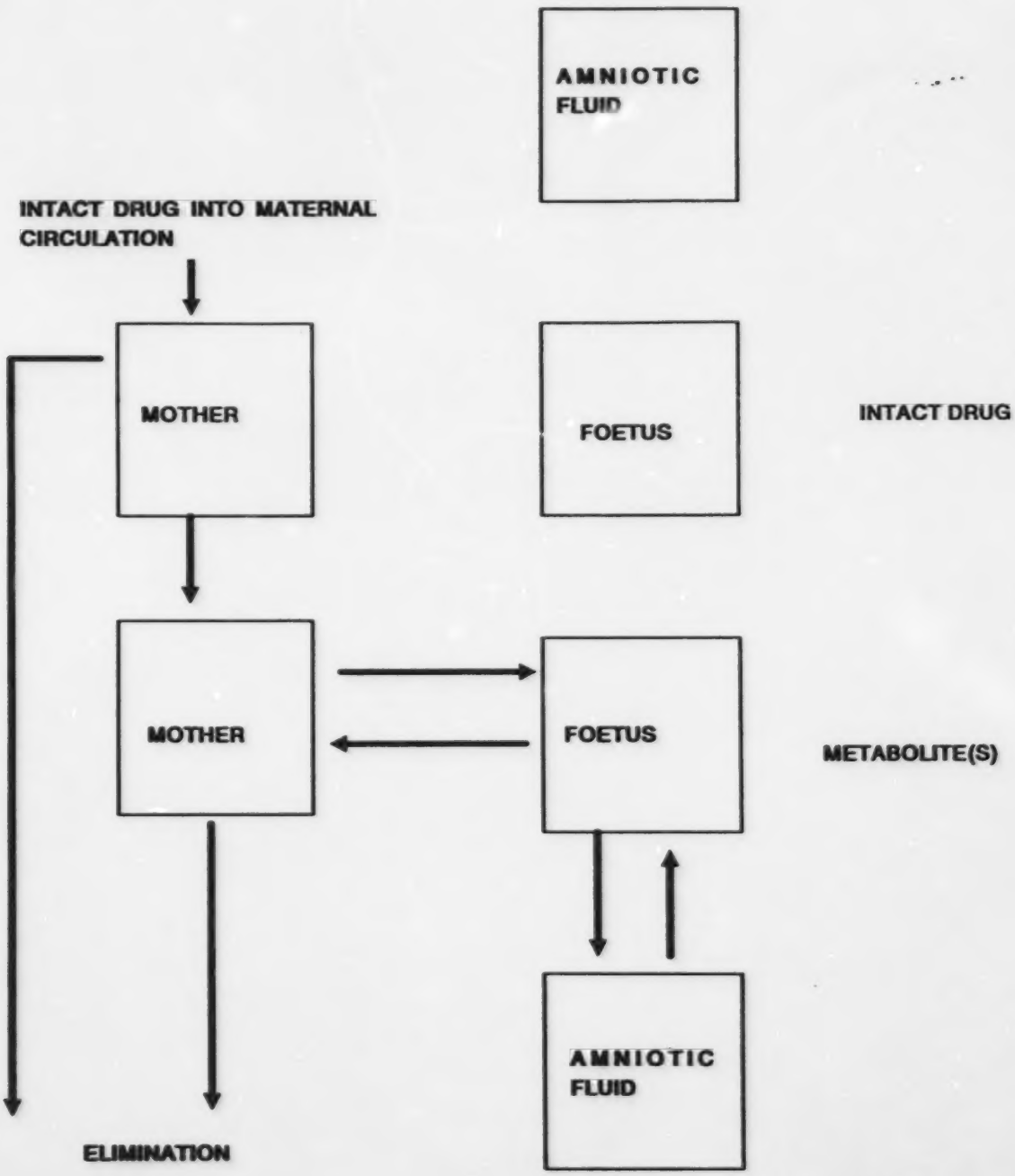


FIGURE 3

# RADIOPHARMACEUTICALS THAT DO NOT CROSS THE PLACENTA

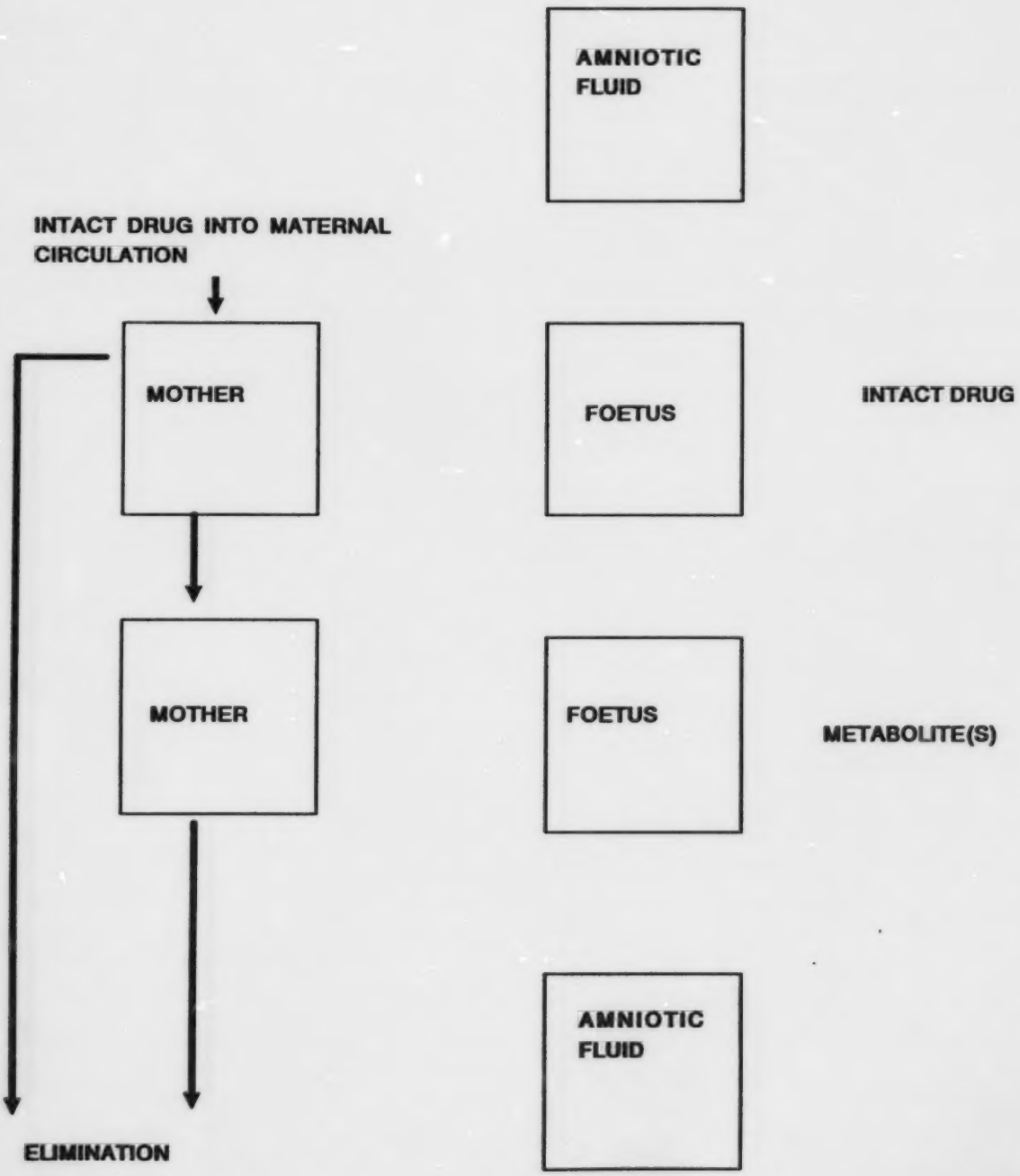


FIGURE 4

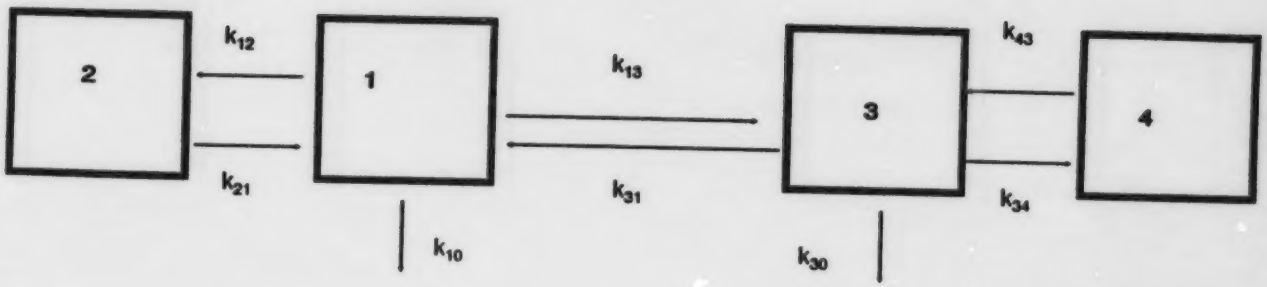


*Figure 5* *The General Model*

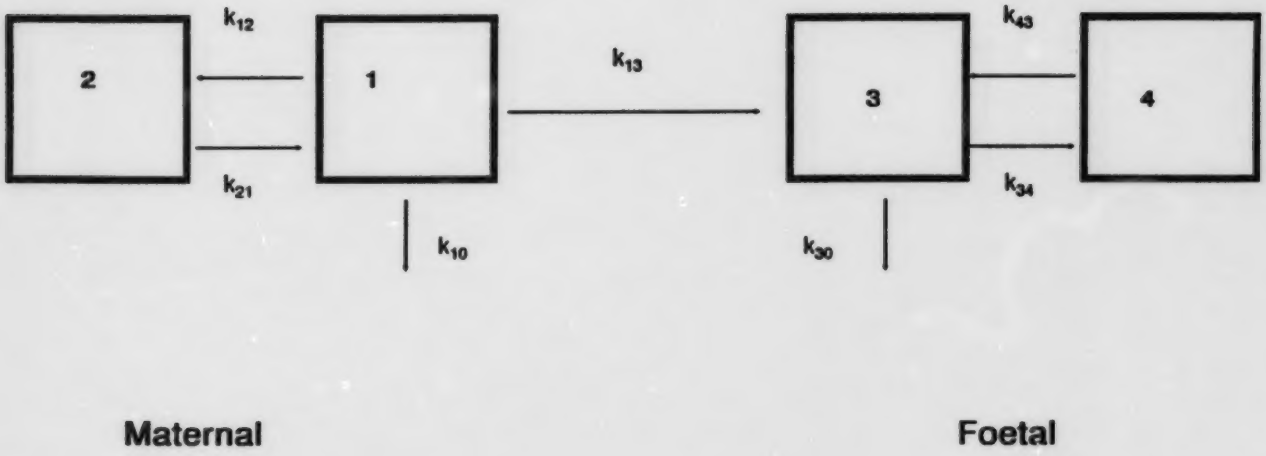


*Figure 6 Unidirectional Diffusion Into the Foetus*

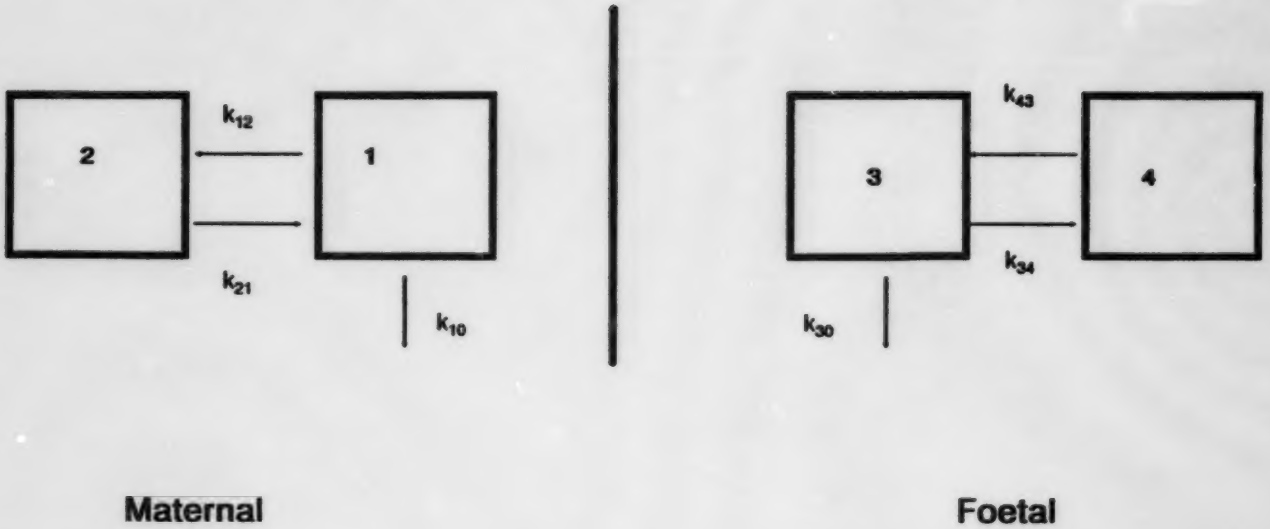


*Figure 7* *No Diffusion or Transport*

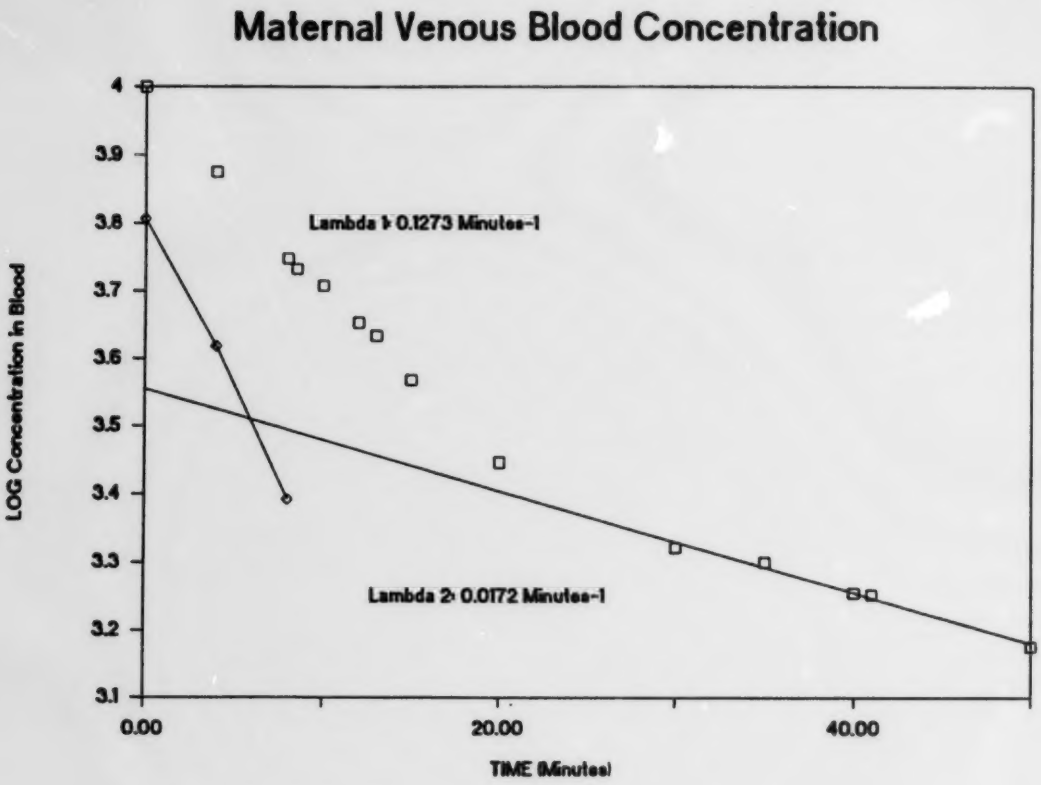
Maternal Venous Blood Concentration
LOG Concentration in Blood
4
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
Lambda 1: 0.1273 Minutes-1
Lambda 2: 0.0172 Minutes-1
0.00
20.00
40.00
TIME (Minutes)

Figure 8.

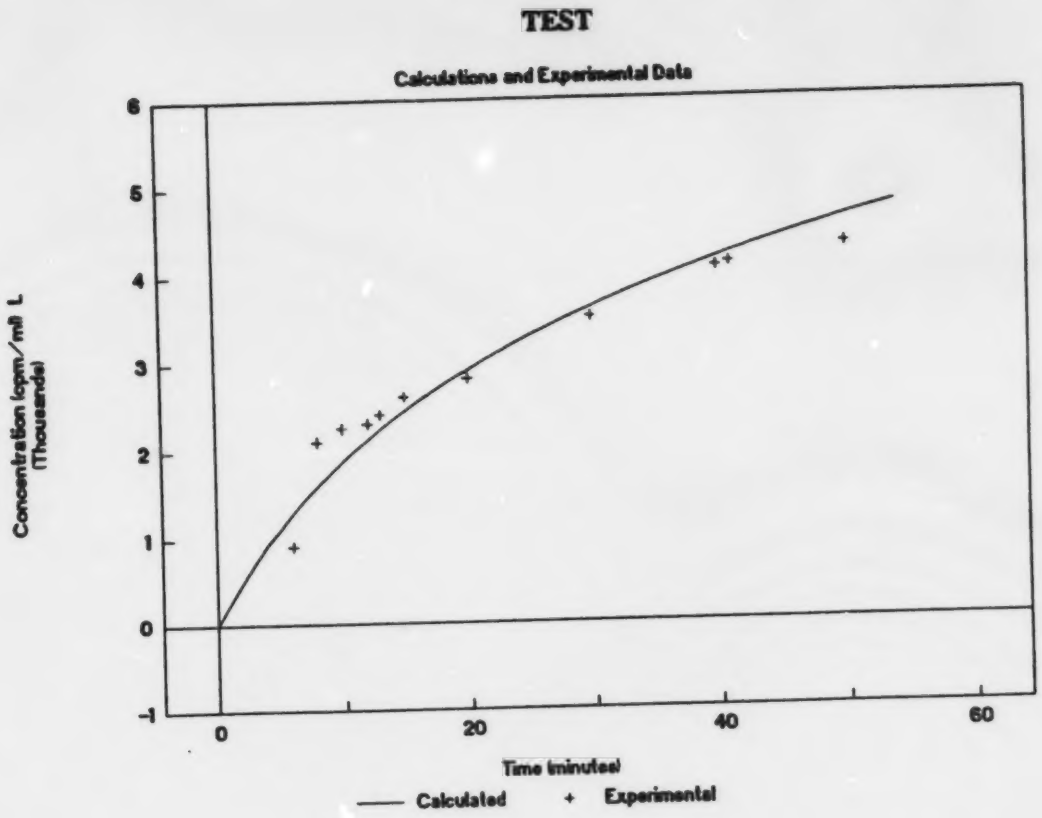
TEST
Calculations and Experimental Data
Concentration (cpm/ml L (Thousands)
6
5
4
3
2
1
0
-1
0
20
40
60
Time (minutes)
Calculated
Experimental

Figure 9.

# TABLE I MATERNAL–FOETAL EXCHANGE REFERENCE SUMMARY

| Radiopharmaceutical | Database Code Number | Maternal References | Foetal References | Kinetics References | Distribution References | Total References |
|---|---|---|---|---|---|---|
| No Drug (Information References) | 000 | 17 | 19 | 6 | 8 | 50 |
| Sodium Pertechnetate Tc-99m | 001 | 3 | 3 | 12 | 22 | 40 |
| Tc-99m Albumin Macroaggregates | 002 | 4 | 1 | 4 | 5 | 14 |
| Tc-99m Sulphide Colloid | 003 | 1 | 1 | 1 | 1 | 4 |
| Tc-99m Methylene Diphosphonate | 004 | 1 | 1 | 6 | 18 | 26 |
| Tc-99m Glucoheptonate | 005 | 0 | 0 | 2 | 2 | 4 |
| Tc-99m DTPA | 006 | 4 | 4 | 8 | 12 | 28 |
| Tc-99m HIDA | 007 | 1 | 1 | 0 | 1 | 3 |
| Tc-99m Albumin | 009 | 3 | 3 | 5 | 7 | 18 |
| Tc-99m Pyrophosphate | 011 | 0 | 0 | 2 | 2 | 4 |
| Sodium Iodide I-131 | 030 | 17 | 11 | 6 | 8 | 42 |
| Sodium Iodohippurate I-131 | 036 | 1 | 1 | 2 | 2 | 6 |
| I-131 Albumin | 037 | 2 | 2 | 1 | 3 | 8 |
| I-131 Iodomethylnorcholesterol | 039 | 7 | 8 | 2 | 7 | 24 |
| I-125 Fibrinogen | 050 | 1 | 1 | 2 | 1 | 5 |
| Ga-67 Gallium Citrate | 090 | 2 | 2 | 1 | 3 | 8 |
| Tl-201 Thallous Chloride | 091 | 3 | 3 | 2 | 3 | 11 |
| In-111 Chloride | 097 | 1 | 2 | 1 | 2 | 6 |
| Xe-133 Xenon Gas | 119 | 2 | 3 | 5 | 4 | 14 |
| F-18 FDG | 120 | 0 | 0 | 1 | 0 | 1 |
| Miscellaneous | 199 | 1 | 1 | 1 | 1 | 4 |
| Totals | | 71 | 67 | 70 | 112 | 320 |

**NOTE:**
***This represents the total number of references to the item NOT the total number of citations.***

## APPENDIX A

This Appendix comprises an alphabetized list of the articles placed in the database. This does not include many of the texts and other documents examined. The references have not been corrected for "format".


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## APPENDIX B

The differential equations which describe the general model may be written.

For the maternal side:

Compartment 1

$$\frac{dX_1}{dt} = k_{21}X_2 + k_{31}X_3 - (k_{12}+k_{13}+k_{10})X_1 \qquad \text{(1A)}$$

Compartment 2

$$\frac{dX_2}{dt} = k_{12}X_1 - k_{21}X_2 \qquad \text{(1B)}$$

For the foetal side:

Compartment 3

$$\frac{dX_3}{dt} = k_{13}X_1 + k_{43}X_4 - (k_{34}+k_{31}+k_{30})X_3 \qquad \text{(2A)}$$

Compartment 4

$$\frac{dX_4}{dt} = k_{34}X_3 - k_{43}X_4 \qquad \text{(2B)}$$

Laplace transforms were used to solve these equations in a similar manner to that for the unidirectional flow model. Values for $A_1$ to $A_8$, $\alpha_1$ to $\alpha_4$, and $\beta_1$ to $\beta_4$ relative to the microconstants were determined and are as follows:

$$A_1 = \frac{X_o}{V_1} \frac{(k_{21}-\alpha_1)(\beta_3-\alpha_1)(\beta_4-\alpha_1)}{(\alpha_2-\alpha_1)(\alpha_3-\alpha_1)(\alpha_4-\alpha_1)} \quad (1)$$

$$A_2 = \frac{X_o}{V_1} \frac{(k_{21}-\alpha_2)(\beta_3-\alpha_2)(\beta_4-\alpha_2)}{(\alpha_1-\alpha_2)(\alpha_3-\alpha_2)(\alpha_4-\alpha_2)} \quad (2)$$

$$A_3 = \frac{X_o}{V_1} \frac{(k_{21}-\alpha_3)(\beta_3-\alpha_3)(\beta_4-\alpha_3)}{(\alpha_1-\alpha_3)(\alpha_2-\alpha_3)(\alpha_4-\alpha_3)} \quad (3)$$

$$A_4 = \frac{X_o}{V_1} \frac{(k_{21}-\alpha_4)(\beta_3-\alpha_4)(\beta_4-\alpha_4)}{(\alpha_1-\alpha_4)(\alpha_2-\alpha_4)(\alpha_3-\alpha_4)} \quad (4)$$

$$A_5 = \frac{X_o}{V_3} \frac{k_{13}(k_{43}-\alpha_1)(k_{21}-\alpha_1)}{(\alpha_2-\alpha_1)(\alpha_3-\alpha_1)(\alpha_4-\alpha_1)} \quad (5)$$

$$A_6 = \frac{X_o}{V_3} \frac{k_{13}(k_{43}-\alpha_2)(k_{21}-\alpha_2)}{(\alpha_1-\alpha_2)(\alpha_3-\alpha_2)(\alpha_4-\alpha_2)} \quad (6)$$

$$A_7 = \frac{X_o}{V_3} \frac{k_{13}(k_{43}-\alpha_3)(k_{21}-\alpha_3)}{(\alpha_1-\alpha_3)(\alpha_2-\alpha_3)(\alpha_4-\alpha_3)} \quad (7)$$

$$A_8 = \frac{X_o}{V_3} \frac{k_{13}(k_{43}-\alpha_4)(k_{21}-\alpha_4)}{(\alpha_1-\alpha_4)(\alpha_2-\alpha_4)(\alpha_4-\alpha_4)} \quad (8)$$

Where:

$$\alpha_1+\alpha_2+\alpha_3+\alpha_4 = \beta_1+\beta_2+\beta_3+\beta_4 \quad (9)$$

$$\alpha_3\alpha_4+\alpha_1\alpha_2+\alpha_1\alpha_4+\alpha_1\alpha_3+\alpha_2\alpha_3+\alpha_2\alpha_4 = \beta_3\beta_4+\beta_1\beta_2+\beta_1\beta_4+\beta_1\beta_3+\beta_2\beta_3+\beta_2\beta_4-k_{13}k_{31} \quad (10)$$

$$\begin{aligned}\alpha_1\alpha_3\alpha_4+\alpha_2\alpha_3\alpha_4+\alpha_1\alpha_2\alpha_3+\alpha_1\alpha_2\alpha_4 \\ = \beta_1\beta_3\beta_4+\beta_2\beta_3\beta_4+\beta_1\beta_2\beta_3+\beta_1\beta_2\beta_4 \\ -k_{43}k_{13}k_{31}-k_{21}k_{13}k_{31}\end{aligned} \tag{11}$$

$$\alpha_1\alpha_2\alpha_3\alpha_4 = \beta_1\beta_2\beta_3\beta_4-K_{13}K_{31}K_{43}K_{21} \tag{12}$$

and:

$$\beta_1+\beta_2 = k_{21}+k_{12}+k_{13}+k_{10} \tag{13}$$

$$\beta_1\beta_2 = k_{21}(k_{13}+k_{10}) \tag{14}$$

$$\beta_3+\beta_4 = k_{43}+k_{31}+k_{34}+k_{30} \tag{15}$$

$$\beta_3\beta_4 = k_{43}(k_{31}+k_{30}) \tag{16}$$

## APPENDIX C

For the maternal portion of the uni-directional model the differential equations may be written for compartments 1 and 2 (1A and 1B)

$$\frac{dX_1}{dt} = k_{21}X_2 - (k_{12}+k_{13}+k_{10})X_1 \qquad (1A)$$

$$\frac{dX_2}{dt} = k_{12}X_1 - k_{21}X_2 \qquad (1B)$$

Laplace transformation of the above equations yields:

$$s\overline{X_1} - X_0 = k_{21}\overline{X_2} - (k_{12}+k_{13}+k_{10})\overline{X_1} \qquad (2A)$$

$$s\overline{X_2} = k_{12}\overline{X_1} - k_{21}\overline{X_2} \qquad (2B)$$

Rearranging equations 2A and 2B yields:

$$(s+k_{12}+k_{13}+k_{10})\overline{X_1} = k_{21}\overline{X_2} + X_0 \qquad (3A)$$

$$k_{12}\overline{X_1} = (k_{21}+s)\overline{X_2} \qquad (3B)$$

Multiplying 3A by $s+k_{21}$ and 3B by $k_{21}$ gives:

$$(s+k_{21})(s+k_{12}+k_{13}+k_{10})\overline{X_1} = (s+k_{21})k_{21}\overline{X_2} + (s+k_{21})X_0 \qquad (4)$$

$$k_{12}k_{21}\overline{X_1} = (s+k_{21})k_{21}\overline{X_2} \qquad (5)$$

and subtracting equation 5 from 4 leads to:

$$[(s+k_{21})(s+k_{12}+k_{13}+k_{10}) - k_{12}k_{21}]\overline{X_1} = (s+k_{21})X_0 \qquad (6)$$

Solving for $X_1$ gives:

$$\overline{X_1} = \frac{(s+k_{21})X_0}{s^2+s(k_{12}+k_{13}+k_{10}+k_{21}) + k_{21}(k_{13}+k_{10})} = \frac{(s+k_{21})X_0}{(s+\lambda_1)(s+\lambda_2)} \quad (7)$$

the inverse transform of which is:

$$X_1 = \frac{X_0(k_{21}-\lambda_1)}{(\lambda_2-\lambda_1)}e^{-\lambda_1 t} + \frac{X_0(k_{21}-\lambda_2)}{(\lambda_1-\lambda_2)}e^{-\lambda_2 t} \quad (8)$$

where:

$$\lambda_1+\lambda_2 = k_{12}+k_{13}+k_{10}+k_{21} \quad (9)$$

$$\lambda_1\lambda_2 = k_{21}(k_{13}+k_{10}) \quad (10)$$

The concentration of the radiopharmaceutical in compartment 1 (ie: maternal blood) is given by:

$$C_1 = \frac{X_1}{V_1} = \frac{X_0}{V_1}\frac{(k_{21}-\lambda_1)}{(\lambda_2-\lambda_1)}e^{-\lambda_1 t} + \frac{X_0}{V_1}\frac{(k_{21}-\lambda_2)}{(\lambda_1-\lambda_2)}e^{-\lambda_2 t} \quad (11)$$

or:

$$C_1 = L_1e^{-\lambda_1 t} + L_2e^{-\lambda_2 t} \quad (12)$$

where:

$$L_1 = \frac{X_o}{V_1}\frac{(k_{21}-\lambda_1)}{(\lambda_2-\lambda_1)} \quad (13)$$

$$L_2 = \frac{X_o}{V_1}\frac{(k_{21}-\lambda_2)}{(\lambda_1-\lambda_2)} \quad (14)$$

A similar but more complicated derivation is used for the foetal compartments 3 and 4 to yield values for $C_3$ the concentration in foetal blood:

$$C_3 = L_3 e^{-\lambda_3 t} + L_4 e^{-\lambda_4 t} + L_5 e^{-\lambda_5 t} + L_6 e^{-\lambda_6 t} \qquad (15)$$

where:

$$L_3 = \frac{k_{13} X_o}{V_3} \frac{(k_{43}-\lambda_1)(k_{21}-\lambda_1)}{(\lambda_3-\lambda_1)(\lambda_4-\lambda_1)(\lambda_2-\lambda_1)} \qquad (16)$$

$$L_4 = \frac{k_{13} X_o}{V_3} \frac{(k_{43}-\lambda_2)(k_{21}-\lambda_2)}{(\lambda_3-\lambda_2)(\lambda_4-\lambda_2)(\lambda_1-\lambda_2)} \qquad (17)$$

$$L_5 = \frac{k_{13} X_o}{V_3} \frac{(k_{43}-\lambda_3)(k_{21}-\lambda_3)}{(\lambda_2-\lambda_3)(\lambda_4-\lambda_3)(\lambda_1-\lambda_3)} \qquad (18)$$

$$L_6 = \frac{k_{13} X_o}{V_3} \frac{(k_{43}-\lambda_4)(k_{21}-\lambda_4)}{(\lambda_2-\lambda_4)(\lambda_3-\lambda_4)(\lambda_1-\lambda_4)} \qquad (19)$$

and:

$$\lambda_3+\lambda_4 = k_{43}+k_{30}+k_{34} \qquad (20)$$

$$\lambda_3\lambda_4 = k_{43}k_{30} \qquad (21)$$